Editorial

Risk of Acute Renal Failure in Angiotensin Converting Enzyme Inhibitor Therapy- An Overview

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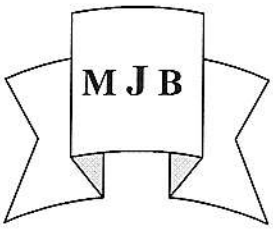

Angiotensin Converting Enzyme Inhibitors (ACEIs) are now in wide use in the treatments of arterial hypertension (HT), congestive heart failure (CHF), Acute myocardial infraction (AMI) as well as diabetic and non diabetic nephropathies. Acute renal failure (ARF) is most likely to occur when renal perfusion pressure can not be sustained either because of critical decrease in mean arterial pressure (MAP) a situation encountered in patients with CHF and pre-existing hypotension and low ventricular filling pressures or when glomerular filtration rate (GFR) is highly angiotensin II (AII) dependent, a situation seen in states of volume depletion and in the presence of high grade bilateral renal artery stenosis as expected in elderly will a great deal of arterial atheromotous disease .

Renal and systemic effects of AII during volume depletion and CHF.

Physiologically renal auto regulation maintains constant renal blood flow (RBF) and GFR over a wide range of MAPS. When renal perfusion pressure (RPP) falls in Hypovolaemia or CHF, sympathetic nervous system activation occurs causing secretion of renin by the juxta glomerular cells of the afferent arterioles with subsequent AII production. AII-induced vasoconstriction of postglomerular efferent arterioles to a greater degree than preglomerular efferent arterioles thus glomerular capillary pressure (GCP) and GFR are restored despite reduced RPP .

AII promotes Na+ retention by the kidney through a number of effects notably increased filtration fraction (GFR / renal plasma flow) direct promotion of proximal tubular Na+ reabsorption and aldoslerone induced Na+ reaasorption by collecting ducts.

Water conservation in these conditions is also stimulated mainly due to Na+ retention, continuing release of ADH and the dipsogenic effect of AII (AII is proved dipsogen that induced thirst through stimulation of central thirst centers).

The physiologically in appropriate thirst drive in CHF is probably explained by AII excess.

These mechanisms fevers restoration of extracelluler volume and maintenance of GFR in volume depleted individuals but in CHF lead to volume expansion in CHF and hyponantraemia which an ominous sign in CHF patients.

Cardiac, renal and systemic haemodynaemic effect of ACE inhibitor therapy of CHF

A uniform reduction in MAP is observed after ACE inhibitor administration due to a reduction in systemic vascular resistance (SVR) similarity a fall in right atrail, pulmonary artery and capillary wedge pressures is noted . The favorable renal effect result from a decrease in total renal vascular resistance and improvement in RBF and an increase in urinary Na+ excretion due to altered glomerular and pertusutar haemodynamic reduced proximal tusular Na+ reabserption and reduced aldersterene dependent collecting duct Na+ reabsorption moreover, an improvement in hyponatraemia may be noted presumably because the dipsogenic effect and vasopressin – releasing effect of AII is lessened in conjunction with improved renal handling of water. Finally the improvement in renal haemodynamic does not result in an increase in GFR and indeed GFR may show some reduction and a slight – (<10-20%) but non progressive rise in serum creatinine concentration and this is due to the relatively greater effect of the ACE inhibitor dilating postglomerular efferent than afferent – arterioles with resultant reduction in glomerular capillary pressure so a small rise in creatinine conc. should not cause on alarm and simply reflect the beneficial effect of ACE inhibitors on renal haemodynaemics. These beneficial effects are seen as long as MAP does not fall below 60-65 mm Hg_,sgnificant renal artery disease_is not present, diuretic – induced volume depletion is not excessive and cardiac output is adequate.

Mechanism of ARF induced by ACE inhibitor therapy

ARF defined as abrupt reduction in renal function usually heralded by a rise in serum creatinine (CR) concentration (Conc.) for practical purposes an increase of ≤0.5mg (44μmol/l) if serum CR was initially<2.0mg/L or increase of 1.0 mg/dl if serum CR was above 2.0mg/dL.

Renal function can deteriorate either acutely on the initiation of ACE inhibitor therapy or in patient receiving chronic ACE inhibitor therapy. Multivariate analysis of various studies revealed that older age, diuretic therapy and diabetes were associated with decreased renal function but B- blocker therapy and higher ejection fraction are Reno protective .

The clinical settings in which ARF is likely precipitated during ACE inhibitor therapy are firstly critical fall of MAP to levels that can not adequately sustain renal perfusion or that provoke substantial reflex activation of renal sympathetic nerves .

ACEIs then will result in a sudden decline in AII levels, an increase in vasodilatory prostaglandins and/or a reduction in total SVR with consequently marked drop in renal perfusion pressure leading to ARF. The situation is compounded by in ability of the heart to raise cardiac output as in advanced cardiomyopathy and prolonged half – life of the administered ACEI if it is one of long acting agents or improved clearance in case of longstanding renal insufficiency. Secondly volume depleted patients from excessive diuretic therapy. Man dal et al reported that 33% of patient with CHF on diuretic therapy developed ARF when ACEIs were administered compared with only 2.4% of patient who were not taking diuretics. Indeed serum CR Conc. returned to pretreatment level when salt intake was liberalized and diuretic doses were reduced . Thirdly ACEIs may induce ARF in patient with high grade bilateral renal artery glanosis or stenosis of a dominant or a single kidney as in renal transplant or with wide spread a atherosclerotic disease in smaller preglomerular vessels result or in patient with afferent arteriolar narrowing due to hypertension or chronic cyclosporine therapy.

Fourthly ACEI may precipitate ARF in patients who are taking agents with vasoconstrictive effect notably non steroidal anti inflammatory agents (NSAIDs) or cyclosporine. Finally risk of ACIEs induced ARF is higher in patients with chronic renal insufficiency than in patients with normal renal function, however ACEI have long term Reno protective effects in those patients due to reversal of the glomerular hyper filtration response of the surviving nephrones as an adoptive changer to maintain GFR. The reversal is achieved by a predominant efferent arteriolar vasodilatation with a decline in glomerular capillary pressure. Therefore a temporary and mild fall in GFR and small rise in serum CR conc. and urea nitrogen is expected and considered as indication that ACEI exerting their desired actions.

Management of ARF during ACE inhibitor therapy

Judicious monitoring of ACEI therapy particularly in CHF is essential if irreversible renal tubular damage caused by an ACEI induced ARF episode is to be prevented. Patients who are at risk developing this form of ARF need to be identified early. Serum CR. and electrolytes should be evaluated before and after 1 week therapy with ACEI is began in CHF patients. Blood pressure (BP) and urine output is monitored and significant drop in BP and oliguria if sustained are indications to withhold ACEIs .

Such response is anticipated in hyponatreamic patient with CHF in whom the rennin angiotensin axis typically excessively activated. Level of serum CR is another guide and a rise of >0.5 mg /dL if initial CR< 2.0mg/dL or a rise of >1.0mg/dL if base line CR >2.0mg/dL also.

Moreover in steady state doubling of serum CR. represent a 50% decrease in CR. clearance such changes especially if become progressive should call for prompt consideration of discontinuing ACEIs and further renal evaluation is undertaken. Renal artery stenosis and micro vascular renal diseases are not uncommon in CHF patient and need to be identified.

ARF complicating ACEI therapy is almost always reversible if the loss of GFR is due to inadequate glomerular capillary pressure which is easily restored as soon as sufficient AII is produced and renal function if tubular damage has not yet occurred will improve within 2-3 days after cessation of ACEI therapy. AII receptor antagonists (AII receptor blocker) should not the substituted as they exert similar effects on renal haemodynamics, in settings were volume depletion is a major factor in the genesis of ACEI induced ARF, repletion of intracellular fluid volume and discontinuation of diuretictherapy is an effective approach although some experts recommend temporary withdrawal of ACEI drugs and of interacting drugs like NSAIDS, adequate fluid and electrolytes balance and temporary dialysis if indicated are main stays of treatment.

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